REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office action dated September 26, 2002, are respectfully requested. The applicants petition the Commissioner for a three-month extension of time: a separate petition accompanies this Amendment.

I. Amendments

Claims 1-14 have been cancelled. New claims 15 to 38 have been introduced to more clearly recite the features of the method of the invention, and to include claims to particular embodiments. The claims find support in the language of the application as originally-filed.

The specification has been amended to provide updated priority information for the instant application.

No new matter has been introduced as a result of these amendments.

II. Double Patenting

The Examiner has rejected claims 1-14 under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-18 of U.S. Patent No. 5,928,469.

The Examiner has also rejected claims 1-14 under the judicially created doctrine of obviousness-type double patenting as unpatentable over the claims of U.S. Patent No. 6,071,428.

In response to this rejection, an executed terminal disclaimer in compliance with 37 C.F.R. §1.32(c) is enclosed herewith.

III. Rejections Under 35 U.S.C. §102(b)

The Examiner has rejected the claims in the instant application as anticipated under 35 U.S.C. §102(b).

Specifically, the Examiner has rejected claims 1-7, 10, 11, 13 and 14 under 35 U.S.C. §102(b) as being anticipated by van de Beek, *et al.* in light of Roos and European Patent Application No. 0 383 569.

The Examiner has also rejected claims 1-4, 6, 8-11, 13 and 14 under 35 U.S.C. §102(b) as

being anticipated by Prajapati, *et al.*

The Examiner has rejected claims 1-7, 10, 11, 13, and 14 under 35 U.S.C. §102(b) as anticipated by Okura Seiyaku.

Finally, the Examiner has rejected claims 1-7 and 10-14 under 35 U.S.C. §102(b) as anticipated by U.S. Patent No. 3,202,731 in light of Klech et al.

These rejections are traversed in view of the newly presented claims, following arguments and supporting case law.

A. The Cited Art

1. Van de Beek, *et al.* Van de Beek describes the effects of spray drying and heating of solutions of the enzyme, rennin. Most relevant to the claims under examination is the description of experiments related to spray drying. In sum, van de Beek describes the loss of activity of rennin upon spray drying aqueous solutions of rennin in combination with various additives including sucrose, urea, sodium chloride, sodium benzoate, and lactose. Specific formulation data coupled with results for residual activity immediately after spray drying is provided in Table 1. Regarding storage stability, van de Beek addresses the subject in only one sentence on page 49, section 3.2, stating, "Spray dried rennin powders containing sucrose and lactose were stored at room temperature. After 250 days there was no loss of biological activity". No further specifics regarding the particular compositions stored are provided.

2. Prajapati, *et al.* Prajapati is directed to spray-drying *lactobacillus acidophilus* LB1H3 in a slurry of fermented milk with various additives including banana, tomato juice, and sugar. More specifically, Prajapati describes the survival rate of LB1H3 upon spray drying and during ambient storage for 2 months.

3. Okura Seiyaku KK, (Okura) This abstract describes spray drying serrapeptidase with various protecting substances including lactose, dextran, dextrin, mannitol, etc. Okura states therein, "the powdered serrapeptidase does not lose its activity even when stored for a long period of time".

4. U.S. Patent No. 3,202,731, (Grevenstuk). Grevenstuk describes a method for forming solid spherical particles from an aqueous emulsion or solution containing a biologically valuable substance and a film-forming colloid. More specifically, Grevenstuk describes a method wherein an aqueous solution or emulsion of the above-described components is first atomized to form drops which are then forced to impinge upon a fluidized bed to thereby solidify the drops into solid spherical particles.

B. The Claimed Invention

The present invention, as embodied in independent claim 15, is based upon the Applicant's recognition that active substances that, on their own, are not stable upon storage at ambient temperature can be rendered storage stable by spray drying in the presence of a glass former to form *glassy* particles having a glass transition temperature above 30° C. Specifically, the method of the invention comprises the following steps:

a. providing an aqueous mixture of a pharmacologically active, therapeutic material selected from the group consisting of proteins, peptides, nucleosides, nucleotides, dinucleotides, and oligonucleotides, and a carrier that is water-soluble or water-swellable, and, that when anhydrous, can exist as a glass with a glass transition temperature (Tg) above about 20° C,

b. spraying into a hot gas stream at an inlet temperature from 80° C to 300 ° C droplets of the aqueous mixture from (a),

c. drying said droplets by passage through said gas stream to form a powder,

d. optionally subjecting the powder from (c) to further drying, to thereby obtain as a result of steps (a) through (c), a glassy powder having a moisture content from about 3% to about 9% by weight and a Tg above about 30° C.

C. Argument

1. Relevant Law.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference" *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d, 628, 631, 2 USQP2d 1051, 1053 (Fed. Cir. 1987).

"The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic", *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981).

"In relying upon the theory of inherency, the Examiner must provide a basis in the fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the prior art." *Ex parte Tanksley,* 37 USPQ 2d 1382, 1385.

"Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency." *Continental Can Co. v. Monsanto Co.,* 948 F.2d 1264, 1269 20 USPQ, 2d 1746, 1749 (Fed. Cir. 1991).

2. Analysis

A. The cited references are first considered with respect to whether their disclosures each teach each and every element of the claimed method.

Looking first at Van de Beek, Van de Beek describes spray drying of rennin, a clotting enzyme found in milk. First, to the best of the undersigned's knowledge, rennin is not a therapeutic protein, and thus does not fall within the scope of the claimed method. Secondly, nowhere does Van de Beek describe drying to obtain a product having a moisture content of 3 to 9 percent by weight. Thirdly, the spray dried compositions of Van de Beek are not necessarily glassy powders, for reasons to be discussed in greater detail below.

Turning now to Prajapati, et al., this reference teaches spray drying of a particular strain of *Lactobacillus acidophilus.* Since the bacterium, *Lactobacillus acidophilus* LB_1H_3, is not therapeutic material selected from the group consisting of proteins, peptides, nucleosides, nucleotides, dinucleotides, and oligonucleotides, the teachings of this reference cannot be said to

anticipate the claimed method.

Okura does not teach the step of drying to obtain a product having a moisture content of 3 to 9 percent by weight.

Lastly, nowhere does Gravenstuk teach the step of drying of atomized droplets of an aqueous mixture by passage through a heated gas stream to form a powder. Rather, Gravenstuk teaches solidification of an atomized solution by allowed the solution to impinge upon a fluidized bed of a solid lubricant. Moreover, nowhere does Gravenstuk teach drying to form a powder having a moisture content of 3 to 9% by weight.

For these reasons alone, the claimed method cannot be said to be anticipated by any of the above-references.

B. Two of the references, Van de Beek and Okura, are further characterized to address the assertion of inherency of the claimed method with respect to formation of a glassy powder.

In keeping with the tenants of the above case law, the question to be addressed in this analysis is as follows, "Would the claimed invention *invariably result* from each of the cited prior art disclosures?" If the answer is no, then the present invention cannot be considered to lack novelty in view of these references.

It is the Examiner's view that the spray-dried particles in each of the cited references would inherently be in a glassy state. The applicants disagree.

First, in considering van de Beek, van de Beek discloses various spray dried formulations of rennin in combination with sucrose, sodium chloride, sodium benzoate, urea, and lactose. The mere fact that the rennin formulations of van de Beek are spray-dried is in no way a guarantee that the resulting formulations are glassy. That is to say, spray drying does not necessarily result in glassy powders. The formation of a glass upon spray drying depends upon many factors, such as (i) the percent moisture, (ii) the number and types of components of the mixture, (iii) the relative amounts of mixture components, (iv) spray drying conditions (e.g., drying rate, temperature of the collector, etc.), and (v) each of the excipient(s) and their tendency towards crystal formation. While spray dried formulations containing an active and at least one glass former are often glasses, they are not necessarily so. Moreover, the *ability* of a glass former such as lactose or sucrose to exist in

a glassy state is in no way an indication that a resulting spray-dried composition containing the glass former and an active will necessarily be glassy.

Looking at the additives taught by van de Beek, both sucrose and lactose are indeed carriers that are capable of forming glasses. Each, when on its own in an anhydrous state, possesses a glass transition temperature greater than 20°C. However, both sucrose and lactose can also exist in a crystalline state - thus spray dried formulations containing these carriers are not necessarily glassy. In further support of this point, enclosed are Exhibits A-D. Exhibit A (Hancock, et al.) describes the spontaneous crystallization of amorphous pharmaceutical sugars, sucrose, lactose, trehalose, and raffinose, under certain conditions. Exhibit B (Saliki-Gerhardt, et al.) describes crystallization of sucrose from the amorphous state. Exhibit C (Sun, et al.) describes phase separation and crystallization in amorphous formulations of glucose-6-phosphate dehydrogenase combined with glucose/sucrose and glucose/trehalose. Exhibit D (Sebhatu, et al.) describes spray-dried lactose that is only 15% amorphous, and further describes transformation of the amorphous regions of lactose to a rubbery state (setting up conditions for crystallization). Thus, it cannot be concluded that the spray-dried formulations of van de Beek are necessarily glassy.

In turning now to Okura, Okura describes spray drying serrapeptidase with a protecting substance. Protecting substances are stated to be lactose, dextran, dextrin, mannitol, lactose, etc. The protecting substance is present in the dried product in 0.5-1 part-by-weight per 1 part-by-weight serrapeptidase. For the reasons set forth above, although the formulations of Okura are composed of a glass former and an active agent, they are not necessarily glasses. Further to that point, and in addition to evidence provided in Exhibits A-D, Exhibit E (Costantino, et al.) describes spray-dried formulations of an anti-IgE monoclonal antibody with mannitol that are prone to mannitol crystallization. These exhibits, when considered either singly or cumulatively, all point to the fact that formation of a glass upon spray drying a formulation containing a glass former is not a foregone conclusion, but rather depends upon a number of factors.

Lastly, when considering the spray dried formulations of the prior art, the Examiner has assumed that such formulations would necessarily possess a certain a glass transition temperature falling within the scope of the Applicant's claims - based solely upon the Tg of the glass former present. This assumption is flawed for the following reasons. The glass transition temperature of

spray dried particles will depend upon at least (i) the Tgs of each of the formulation components, (ii) relative amounts and physical state of each of the formulation components, and (iii) the amount of moisture in the sample. To illustrate this point, enclosed is Exhibit F (Schubnell, et al.) which demonstrates a variation (drop) of 50°C in glass transition temperature of a spray dried pharmaceutical formulation in the presence of only 6% moisture. Thus, while one can favor the formation of a spray-dried composition having a relatively high glass transition temperature by the selection or use of glass formers having high Tgs, the Tg of the resultant composition cannot typically be predicted based solely on limited formulation information.

In sum, there is a reasonable likelihood, based at least on the evidence provided in Exhibits A-F and the arguments provided herein, that the formulations of the prior art are, in fact, not glasses. That is to say, formation of a glass is by no means a foregone conclusion for the compositions of the cited art. In the absence of such certainty, the claimed invention cannot be considered to lack novelty in view of the cited art.

IV. Rejections Under 35 U.S.C. §103

The Examiner has rejected claims 1-11 and 13-14 under 35 U.S.C. §103(a) as being unpatentable over European Patent No. 0,383,569 in view of van de Beek, *et al.*

The Examiner has also rejected claims 1 and 12 under 35 U.S.C §103(a) as being unpatentable over EP '569 in view of van de Beek and U.S. Patent No. 3,617,302 in light of Klech.

These rejections are respectfully traversed in view of the following remarks.

A. Cited Art

1. Van de Beek is characterized in section III.A above.

2. Franks, F., *et al.*, EP Patent Publication 0 383 569 (EP '569). Franks describes a method in which biochemical and pharmaceutical materials which tend to be unstable when stored in solution are rendered stable by incorporating such materials into an amorphous, glassy matrix.

Processes described in Franks for preparing a glassy composition include (i)

homogenizing an aqueous solution of an active material with a glassy carrier to form a dough, rolling or milling the dough, followed by vacuum removal of water, (ii) vacuum removal of water from an aqueous solution of the glass former and the active material, and (iii) addition of a dry, glassy carrier to an active material.

Nowhere does Franks teach or suggest spray-drying for preparing glassy compositions of the type claimed.

3. Collins, T.W. (U.S. Patent No. 3,617,302). Collins describes a method for providing flowable, particulate food compositions containing a liquid or liquifiable material such as a fat. Specifically, a solid carrier (e.g., edible proteins and carbohydrates) which has been treated, e.g., by gas injection spray drying, to possess an expanded, substantially spherical structure, is added to a liquid material by mechanical mixing to provide a flowable, particulate composition.

Collins has nothing to do with rendering storage stable active materials of the type encompassed by the present claims, by incorporation into a glassy phase or by any other method. Rather, Collins is concerned with food products and methods for providing flowable food compositions. Moreover, Collins describes a method in which a carrier, by itself, is gas injection spray-dried for the purpose of forming low density, spherical *carrier* particles. Collins does not spray dry a carrier in combination with an active agent, nor is Collins concerned with forming glassy particles, for any purpose.

4. Klech, et al. Klech provides an investigation of the swelling rates of a glassy polymer matrix, such as the type used in a swelling controlled drug delivery system, at various loads of the drug, isoniazid. Isoniazid is a small molecule, not an active material of the type encompassed by the claimed invention.

In looking at the reference as a whole, this reference has nothing to do with rendering storage stable a compound that could not otherwise be stably stored at ambient temperature. Moreover, this reference has nothing to do with forming glassy powders of the type of the present invention, by spray drying or by any other method. Rather, this reference is directed to the factors affecting release of a drug incorporated into a glassy polymer

matrix.

B. Analysis: No Motivation to Modify/Combine the Prior Art

1. Applicable Case Law

"Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention when there is some teaching, suggestion, or motivation to do so found in either the references themselves of in the knowledge generally available to one of ordinary skill in the art." *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

"In determining the propriety of the Patent Office case for obviousness, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination or other modification". *In re Linter,* 458 F.2d 1013, 1016, 173 USPQ 560, 562.

"The mere fact that the references can be combined or modified does render the resultant combination obvious unless the prior art also suggests the desirability of the combination". In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

2. Rejection of claims under 35 U.S.C. §103(a) over EP '569 in view of Van de Beek

Neither reference, Van de Beek or Franks, provides the slightest motivation for combining the two references to arrive at the applicant's claimed invention. Franks neither teaches nor suggests spray-dried compositions - the point of Franks is the utilization of a *glassy matrix* for rendering storage stable otherwise unstable active materials. Rennin, the subject of van de Beek, is stated to be commercially available in both solution and dry powder forms. Specifically, Van de Beek states on page 46, last paragraph, "Rennin is on the market as an aqueous solution (rennet). For preservation the rennin solution contains 20% NaCl and 1% sodium benzoate. Also rennin is preserved in dried state, mixed with starch in powder or tablet form..." Thus, rennin can hardly be considered a storage unstable material.

Moreover, Franks provides no motivation for one to apply spray drying or spray-drying like techniques, nor does Franks provide any reason to believe that spray-drying would yield stable

glasses of the type presently claimed. Since Franks neither shows nor suggests spray-drying, nor provides any rationale to look to alternative high temperature drying techniques such as spray-drying, there is no motivation for combining the Franks and van de Beek references to arrive at the claimed invention. In fact, in the context of evaporation of solvent under reduced pressure to form glasses, Franks teaches away from the use of high temperatures, stating "typical conditions are to commence the evaporation at a temperature not exceeding 40 °C, preferably in the range from 20 to 30 °C and continue it for some hours, ..." (EP '569, page 5, lines 44-47).

Similarly, for the reasons discussed in section III.A. above, and in particular since van de Beek has nothing to do with glassy compositions, and neither teaches nor suggests the described rennin compositions to be glasses, one skilled in the art, when considering van de Beek, would not be motivated to look to the teachings of Franks, which are directed solely to glassy compositions.

Thus, since neither of the cited art references suggests the desirability of the combination (and thus the obviousness of making the combination), the invention cannot be considered obvious in view thereof.

3. Rejection of claims under 35 U.S.C. §103(a) in view of EP '569 in view of Van de Beek and U.S. Patent 3,617,301 (Collins) in light of Klech.

Collins, directed to specific flowable, particulate food compositions containing edible components, cannot make up for the deficiencies of Franks and van de Beek as set forth above. Nor can Klech. As is the case with Collins, Klech is not at all relevant to the claimed invention. That is to say, neither Collins nor Klech, when considered either singly or in combination, provides a further suggestion or motivation for combining the references to arrive at the claimed method than do either Van de Beek or Franks. Thus, these additional references do not render obvious the combination.

In view of the above remarks, it is submitted that the claims are non-obvious in view of the cited art, and that the rejections under 35 U.S.C. §103 should be withdrawn.

V. Conclusion

In view of the foregoing, the Applicant submits that the claims pending in the application

patentably define over the art of record. A Notice of Allowance is therefore respectfully requested.

If a telephone conference would expedite the prosecution of the subject application, the Examiner is requested to call the undersigned at (650) 631-3100.

Respectfully submitted,
NEKTAR THERAPEUTICS
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Exhibit A

1: Pharm Dev Technol 1999 Jan;4(1):125-31 Related Articles, Books, LinkOut

The effect of temperature on water vapor sorption by some amorphous pharmaceutical sugars.

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To determine the effect of temperature on the water vapor sorption behavior of some amorphous pharmaceutical sugars, aqueous solutions of sucrose, lactose, trehalose, and raffinose were freeze-dried using a conventional laboratory lyophilizer. The amorphous sugars formed were stored for several months at 5, 30, and 50 degrees C and at a range of relative humidities (0-90% RH). After equilibration the extent of water vapor sorption was determined gravimetrically, and the presence of any crystalline material was determined. A significant amount of water was sorbed by each of the amorphous sugars even at moderate humidities. In every system studied, lowering the storage temperature at any given relative humidity caused an increased quantity of water to be sorbed. This indicated the predominance of an exothermic water vapor sorption process. Spontaneous crystallization of all the sugars occurred at elevated RHs, and the onset of crystallization did not necessarily coincide with attainment of the water content of the final crystalline forms(s) or the reduction of the sugars' glass transition temperature to ambient conditions. Notably, the amorphous and crystalline forms of some sugars were able to coexist in a quasi-equilibrium state under certain temperature and humidity conditions.

PMID: 10027221 [PubMed - indexed for MEDLINE]

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Exhibit B

1: Pharm Res 1994 Aug;11(8):1166-73 Related Articles, Books

Non-isothermal and isothermal crystallization of sucrose from the amorphous state.

Saleki-Gerhardt A, Zografi G.

School of Pharmacy, University of Wisconsin-Madison 53706.

The crystallization of a model compound, sucrose, from the amorphous solid state has been studied non-isothermally using differential scanning calorimetry to determine crystallization temperature, Tc, and isothermally at 30 degrees C by subjecting samples to 32.4% relative humidity and gravimetrically monitoring water vapor uptake and subsequent loss with time due to crystallization. From the measurement of glass transition temperature, Tg, and melting temperature, Tm, for sucrose alone and in the presence of absorbed water it was possible to predict Tc and thus to directly relate the plasticizing effects of water to its tendency to promote crystallization. Colyophilization of sucrose with lactose, trehalose, and raffinose, all having Tg values greater than that of sucrose, increased Tc significantly, even at levels as low as 1-10% w/w. In the isothermal studies the time required for crystallization to commence, due to the plasticizing effects of water, i.e., the induction time, assumed to be mostly affected by rates of nucleation, was greatly increased by the presence of the additives at these low levels, with raffinose producing a greater effect than lactose and trehalose. Similarly, these additives reduced the rate of water loss, i.e., the rate of crystal growth, but now no significant differences were noted between the three additives. The possible relationships of nucleation and crystal growth and the effects of additives on molecular mobility are discussed.

PMID: 7971719 [PubMed - indexed for MEDLINE]

Exhibit C

1: Biochim Biophys Acta 1998 Sep 16;1425(1):235-44 Related Articles, Books

Protein inactivation in amorphous sucrose and trehalose matrices: effects of phase separation and crystallization.

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Trehalose is the most effective carbohydrate in preserving the structure and function of biological systems during dehydration and subsequent storage. We have studied the kinetics of protein inactivation in amorphous glucose/sucrose (1:10, w/w) and glucose/trehalose (1:10, w/w) systems, and examined the relationship between protein preservation, phase separation and crystallization during dry storage. The glucose/trehalose system preserved glucose-6-phosphate dehydrogenase better than did the glucose/sucrose system with the same glass transition temperature (Tg). The Williams-Landel-Ferry kinetic analysis indicated that the superiority of the glucose/trehalose system over the glucose/sucrose system was possibly associated with a low free volume and a low free volume expansion at temperatures above the Tg. Phase separation and crystallization during storage were studied using differential scanning calorimetry, and three separate domains were identified in stored samples (i.e., sugar crystals, glucose-rich and disaccharide-rich amorphous domains). Phase separation and crystallization were significantly retarded in the glucose/trehalose system. Our data suggest that the superior stability of the trehalose system is associated with several properties of the trehalose glass, including low free volume, restricted molecular mobility and the ability to resist phase separation and crystallization during storage.

PMID: 9813347 [PubMed - indexed for MEDLINE]

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Exhibit D

1: Pharm Res 1994 Sep;11(9):1233-8

Related Articles, Books

Effect of moisture sorption on tabletting characteristics of spray dried (15% amorphous) lactose.

Sebhatu T, Elamin AA, Ahlneck C.

Department of Pharmacy, Uppsala University, Sweden.

Spray dried (15% amorphous) lactose absorbs moisture when exposed to humidity. At 57% relative humidity (RH), the moisture uptake was 1.5%. It is suggested that the moisture is preferentially taken up in the amorphous regions, thereby increasing the actual moisture content in the amorphous parts up to 10%. The moisture uptake reduced the glass transition temperature below the operating temperature and thereby transformed the amorphous regions from a glassy to a rubbery state, setting up conditions for crystallisation of the lactose. Compaction of dry spray dried lactose led to a relatively low initial tablet strength. However, when pre-exposed to 57% RH for a short time period (2 to 4 hours) before compaction, the initial tablet strength increased markedly. This was due to moisture uptake which resulted in a higher molecular mobility of the amorphous spray dried lactose, and to an increase in plastic flow. Post compaction storage of tablets containing amorphous regions of spray dried lactose at 57% RH resulted in an increased tablet strength after 4 hours due to crystallisation. Spray dried lactose exposed to 57% RH for more than 6 hours before compaction led to the lowest initial tablet strength. Crystallisation of the amorphous regions of the spray dried lactose occurred before tabletting. No increase in tablet strength was noted on post compaction storage for these tablets.

PMID: 7816749 [PubMed - indexed for MEDLINE]

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D

Exhibit E

1: J Pharm Sci 1998 Nov;87(11):1406-11

Effect of mannitol crystallization on the stability and aerosol performance of a spray-dried pharmaceutical protein, recombinant humanized anti-IgE monoclonal antibody.

Costantino HR, Andya JD, Nguyen PA, Dasovich N, Sweeney TD, Shire SJ, Hsu CC, Maa YF.

Pharmaceutical Research and Development, Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, USA.

We have examined the stability and aerosol performance of the pharmaceutical protein recombinant humanized anti-IgE monoclonal antibody (rhuMAbE25) spray dried with mannitol. The aerosol performance was measured by the fine particle fraction (FPF), and stability was assessed by the formation of soluble aggregates. When mannitol was added to the spray-dried rhuMAbE25 formulation, its ability to stabilize the protein leveled off above about 20% (w/w, dry basis). The FPF of the spray-dried formulations was stable during storage for rhuMAbE25 containing 10% and 20% mannitol, but the 30% formulation exhibited a dramatic decrease upon storage at both 5 degreesC and 30 degreesC, due to mannitol crystallization. We tested the addition of sodium phosphate to a 60:40 rhuMAbE25:mannitol (w:w) mixture, which otherwise crystallized upon spray drying and yielded a nonrespirable powder. The presence of sodium phosphate was successful in inhibiting mannitol crystallization upon spray drying and dramatically lowering the rate of solid-state aggregation. However, over long-term storage some crystallization was observed even for the phosphate-containing samples, concomitantly with increased particle size and decreased suitability for aerosol delivery. Therefore, the physical state of mannitol (i.e., amorphous or crystalline) plays a role both in maintaining protein stability and providing suitable aerosol performance when used as an excipient for spray-dried powders. Agents which retard mannitol crystallization, e.g., sodium phosphate, may be useful in extending the utility of mannitol as an excipient in spray-dried protein formulations.

PMID: 9811498 [PubMed - indexed for MEDLINE]

E

Exhibit F

1: Int J Pharm 2001 Apr 17;217(1-2):173-81 Related Articles, Books, LinkOut

Quantitative determination of the specific heat and the glass transition of moist samples by temperature modulated differential scanning calorimetry.

Schubnell M, Schawe JE.

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In differential scanning calorimetry (DSC), remnant moisture loss in samples often overlaps and distorts other thermal events, e.g. glass transitions. To separate such overlapping processes, temperature modulated DSC (TMDSC) has been widely used. In this contribution we discuss the quantitative determination of the heat capacity of a moist sample from TMDSC measurements. The sample was a spray-dried pharmaceutical compound run in different pans (hermetically-sealed pan, pierced lid pan [50 microm] and open pan). The apparent heat capacity was corrected for the remaining amount of moisture. Using this procedure we could clearly identify the glass transition of the dry and the moist sample. We found that a moisture content of about 6.2% shifts the glass transition by about 50 degrees C.

PMID: 11292553 [PubMed - in process]

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